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REVIEW ARTICLE

Lymphangioleiomyomatosis: a review of the literature

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Abstract Lymphangioleiomyomatosis (LAM), characterized by alveolar smooth muscle proliferation and cystic destruction of lung parenchyma, can occur as a rare sporadic disease or as a complication of tuberous sclerosis (TSC). It is a cystic lung disease, usually generalized and progressive, may be extremely difficult to treat and has been considered to have a poor prognosis. It has almost exclusively been reported to present in women of childbearing age, most commonly with dyspnoea and pneumothorax. We reviewed the English literature from 1939 to 1997 for cases of LAM both with and without TSC, in order to document the prevalence, clinical features, investigations, treatment and outcome within and between these two groups. No study has yet determined the prevalence of LAM symptomatically within the general population, but it probably affects 1–3% of the TSC population. Patients with TSC often present with an insidious onset of dyspnoea whilst non-TSC patients present more commonly with acute breathlessness secondary to pneumothorax. Patients with TSC are also less likely to suffer from chylothorax. The age of onset of symptoms and of diagnosis are similar. LAM is rare in children and even less common in males in both groups. The natural course of LAM remains unclear and effect of treatment variable. Although symptomatic LAM is uncommon it causes a significant amount of morbidity and mortality both in the TSC and general population, but asymptomatic LAM is not uncommon in TSC. Further research is required to determine the natural history of this condition and to evaluate current treatment regimes.

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INTRODUCTION

Lymphangioleiomyomatosis (LAM) occurs in association with tuberous sclerosis (TSC) or arises as a single entity. Its pathogenesis remains uncertain but may have a molecular genetic basis. Hamartomas (including lymphangioleiomyomas) arising in individuals with TSC involve tumour suppressor genes with inactivation of both alleles of TSC1 or TSC2 through a germline or early embryonic mutation and a second 'somatic' mutation of the remaining normal gene. A chance double 'somatic' inactivation of both alleles of one TSC gene in an individual without a germline mutation could explain the occurrence of LAM in an individual with no other signs of TSC.

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LAM predominately affects females of childbearing age (1) and is characterized by alveolar smooth muscle proliferation and cystic destruction of the normal lung parenchyma. The commonest presenting symptoms are dyspnoea from pneumothorax and chylothorax, but other symptoms include chronic cough, haemoptysis, wheeze and chest pain. Cyanosis, respiratory failure and cor pulmonale can occur (1–3), but asymptomatic cases have been described (2). Pulmonary function tests can show an obstructive or restrictive pattern (4).

Treatment of LAM is difficult, and it has historically been symptomatic: by drainage of pneumothoraces, use of conventional inhalers for wheeze and oxygen therapy for respiratory failure. More recently, hormone manipulation has been tried but without consistent success (3,5). The long-term prognosis is considered poor with many patients thought to follow a relentless deterioration after the onset of their symptoms (2).

The aims of this study were to document the incidence, prevalence, sex, age, presenting features,

investigations, treatment and outcome of LAM arising in patients 'de novo' and in those with a diagnosis of TSC through a comprehensive review of the literature. Also to compare the finding of these groups and highlight the similarities and differences between them.

METHODS

A search of the English literature for all cases of LAM, both with and without associated TSC, was performed from 1939 to 1997 using the Medline and Embase databases. The references of all retrieved papers (including those discounted after review) were searched for additional references.

The cases were then divided into three groups on the following criteria. TSC: a diagnosis of TSC was stated by the authors, or the authors reported features in the individual(s) which fulfilled contemporary criteria for the diagnosis of TSC (6). Not TSC: the authors stated that the individual(s) did not have any features of TSC. Unknown: the authors did not state whether the individual(s) did or did not have TSC, features suggesting possible TSC may have been described (e.g. mental retardation) but did not fulfil the criteria for a diagnosis of TSC. This last group was then excluded from analysis.

RESULTS

There were 183 papers citing a total of 445 cases of LAM. Eighty-three cases had TSC, 69 did not have TSC. In 293 patients it was not clear if TSC was present or excluded.

In total there were only 10 studies that presented a cohort of patients (8–46 patients). The remaining papers only presented case studies. No study gave an overall estimation of either the incidence or prevalence of LAM in the general population. Two studies did however give an estimation of the prevalence of LAM in patients with TSC. Castro *et al.* (3) undertook a retrospective study over 43 years (1948–1991) of patients attending the Mayo clinic; 388 patients had TSC and nine of these had LAM diagnosed, giving a prevalence of ~2·3%. Dwyer *et al*. (2) gave an estimated prevalence of less than 1%, but they did not say how they reached this conclusion.

There were 435 females, nine males and in one case the gender was not given. Seventy-eight females and five males had TSC, and 68 females and one male were stated as not having TSC. In none of the males in whom LAM was reported were the accounts fully consistent with a diagnosis of LAM (see Table 1). The average age of onset of pulmonary symptoms in the group with TSC was given for 75 patients, mean 30.4 years (range 8–57 years, SD 9·2 years). In the patients without TSC, it was given for 68 cases, mean 34·6 years (range 9–62 years, SD 11·9 years). The age of diagnosis of LAM in the group with TSC was given for 59 patients, mean 36·6 years (range 13–72 years, SD 10·7 years). In the group without TSC, it was given for 29 cases mean 36·6 years (range 8–68 years, SD 12·7 years). The differences were not significant.

The symptoms experienced by each of the two groups and their presenting features are summarized in Table 2. Patients who were known to have TSC were more likely to present with gradual onset of dyspnoea, whilst those not having TSC were more likely to present with a pneumothorax. The commonest reported complications were pneumothorax and chylothorax, this latter being more common in those without TSC. Pleural effusions were also reported but it was not always stated if these were serous, chylous or bloody. Patients with TSC were much more likely to be asymptomatic.

Not all papers stated how a diagnosis of LAM was confirmed but there was no difference in the method of diagnosis used between the two groups (Table 2). Lung function testing was much less likely to have been performed in those patients known to have TSC. No patient with TSC had a mixed picture of obstructive and restrictive impairment compared with 48% of the non-TSC group (Table 2).

Where stated most patients were treated symptomatically. Pnuemothoraces and effusions were drained when

TABLE 1 Details of males with apparent LAM. In none was the findings convincing by modern standards

TSC
Case one had chest X-ray findings compatible with a diagnosis of LAM and a biopsy reported 'as consistent with TSC'
Case two had chest X-ray findings that were not typical of LAM and had not had CT or biopsy performed. It is therefore possible that this patient did not have LAM
Case three had findings typical of LAM on his chest X-ray, but the authors did not state whether the biopsy showed smooth muscle proliferation
Case four was shown to have cysts, both empty and filled on biopsy, but no mention of smooth muscle proliferation
Case five a normal HRCT was reported
Not TSC
This case only had a 'clinical diagnosis' of LAM with no pathological confirmation

Table 2 Symptoms and presenting features, investigations and treatment effects of patients with LAM and with or without TSC

	TSC n = 83	Not TSC N = 69
Symptoms experienced and symptoms at presentation		
Dyspnoea any time:	67%	91%
Dyspnoea at presentation:	38%	20%
Pneumothorax any time:	47%	67%
Pneumothorax at presentation:	29%	68%
Cough any time:	24%	35%
Cough at presentation:	0%	0%
Chylothorax any time:	10%	33%
Chylothorax at presentation:	2%	2%
Haemoptysis any time:	19%	32%
Haemoptysis at presentation:	0%	3%
Respiratory failure any time:	0%	0%
Respiratory failure at presentation:	0%	2%
Pain (without proven pnuemothorax) any time:	6%	2%
Pain (without proven pnuemothorax) at presentation:	0%	0%
Other any time:	2%	3%
Other at presentation:	6%	2%
Asymptomatic	25%	3%
Investigations (for diagnosis)		
Post mortem	9 (10%)	8 (12%)
Biopsy	18 (21%)	16 (23%)
Chest CT	15 (18%)	7 (10%)
Chest X-ray	9 (10%)	4 (6%)
Not reported	32 (39%)	34 (49%)
Pulmonary function tests		
Normal	5(6%)	4 (6%)
Obstructive	18 (22%)	16 (23%)
Restrictive	3 (4%)	1 (1%)
Mixed	0	33 (48%)
Abnormal	8 (10%)	2 (3%)
Not reported	49 (59%)	13 (19%)
Patients who *did* undergo hormonal manipulation		
Improved	6 (33%)	2 (5%)
Stable/unchanged	5 (27%)	9 (21%)
Worsened/died	6 (33%)	23 (55%)
Unknown	1 (5%)	8 (19%)
Total	18	42
Average follow up	5 years	8 years
Patients who *did* not undergo hormonal manipulation		
Improved	0	1 (7%)
Stable/unchanged	6 (24%)	3 (20%)
Worsened/died	19 (76%)	11 (73%)
Total	25	15
Average follow-up not given for this as data not available		

clinically necessary and pleurodesis and pleurectomies were frequently reported. Many patients received courses of antibiotics and those in respiratory failure were treated with oxygen. Hormonal manipulation (including methylprogesterone, tamoxifen, surgical oophorectomy, radioablation of the ovaries, buserelin and LHRH) was tried in a total of 60 (39%) patients with variable success. Follow-up was only reported for 40 (26%) patients who did not receive hormonal treatment (Table 2). Although the trend is that patients undergoing hormonal manipulation (especially those with TSC) had a better outcome than those who did not, the numbers are too small for analysis.

DISCUSSION

Although we divided patients into those who had a definite diagnosis of TSC and those who did not have TSC as defined in the methods, we assumed that the diagnosis of

LAM was correct in all cases but it was not always clear as to how this diagnosis was reached or how unequivocal the diagnosis was and some cases are likely to have been misdiagnosed.

Although LAM predominately affects females of childbearing age, cases occurring in men (7,8) and children (9,10) have, rarely, been reported. In many cases symptoms are exacerbated during the menstrual cycle or in the course of a pregnancy (11,12), and patients have also reported onset of symptoms following the menopause (13,14), or after commencing the oral contraceptive pill (3). It is difficult to estimate the true frequency of LAM in males. It is certainly extremely rare. In any male in whom the diagnosis is suspected, other pulmonary diagnoses must be excluded and the gender should be confirmed by karyotype to rule out Kleinfelter's syndrome. Male patients should have HRCT and lung biopsy performed to confirm the diagnosis.

Although there was no difference between the two groups for average age of onset of pulmonary symptoms and age at diagnosis of LAM, there was a shorter period of delay between onset and diagnosis in the group without TSC. One might expect to make the diagnosis quicker in patients with TSC because of heightened awareness of the possibility of LAM in TSC. Patients who were known to have TSC were more likely to present with gradual onset of dyspnoea, whilst those not having TSC were more likely to present with a pneumothorax. One possible explanation for this might be that patients with TSC are more likely to develop multiple foci of LAM because of their genetic predisposition. As these area slowly increase in both number and size causing destruction of the normal lung parenchyma they result in increasing dyspnoea which is inversely proportional to the volume of normal lung remaining. In patients without TSC a single harmatoma arising as a chance event may remain asymptomatic with the remaining normal lung parenchyma compensating for the single area of abnormality until there is a sudden pneumothorax. No study has reported radiographic imaging to correlate between the size, position or number of the harmatomas and the incidence of pneumothorax. Chylothoraces may occur less commonly in patients with TSC; 10% of cases with proven TSC compared to 33% in patients in whom TSC has been definitely excluded. A possible explanation is found histiologically, as the smooth muscle proliferation in LAM seen in TSC is more frequently described as being predominantly perivascular, whilst in LAM without TSC it is more often described as perilymphatic (3). The reason for the different distribution is not clear. The increased awareness of LAM in TSC might explain the higher number of asymptomatic cases in the TSC group as compared to the group without TSC, but could be a chance finding. There was a wide range of presentation in all four groups. The commonest presenting symptoms were pneumothorax and dyspnoea. Other symptoms included chronic dry cough, haemoptysis, wheeze and chest pain. Development of cyanosis, respiratory failure and cor-pulmonale was also common.

Lung function tests show a wide range of patterns from normal to obstructive through a mixed picture to restrictive. This variation is unsurprising when the underlying pathogenesis is considerly. Initially there is proliferation of smooth muscle cells around the bronchi leading to narrowing of the lumen, as seen in asthma, giving rise to an obstructive picture. However unlike asthma the narrowing is not due to bronchospasm but rather hyperplasia, and the obstruction is not readily reversible. With time air trapping in the alveoli leads to an emphysematous picture with the formation of cysts and bullae giving rise to a restrictive picture. As the disease progresses with more smooth muscle cells surrounding both the airways and the blood vessels diffusion becomes impaired, cor-pulmonale and respiratory failure develop. Patients with TSC were less likely to have their lung function tested than other sufferers of LAM, possibly because about half of patients with TSC have severe learning difficulties and might be unable to co-operate with testing. Although there appeared to be differences between the two groups in terms of lung function with a higher proportion of patients without TSC having a mixed picture. 25 of these patients were from one study which might have used different criteria for measurement to other studies.

Again, because of the rarity of this condition few studies have been performed to assess long-term treatment and indeed few therapeutic measures have been undertaken in order to ameliorate the course of the disease. Instead treatment is symptomatic. The presence of hormonc receptors in the lung tissue of patients with LAM and TSC (16), the suggestion that exacebations can occur at times of hormonal fluctuation, for example during pregnancy and in association with the oral contraceptive pill, and the relative absence of LAM in males have, not surprisingly, led to attempts to ameliorate the disease by hormonal manipulation (17–20). Of cases reported in the literature review under half received hormonal therapy with inconsistent results. The best results appear to be seen in those LAM patients who have TSC. Approximately one-third (6/18) of patients with TSC tried on hormonal therapy showed improvement compared with none (0/25) showing improvement without hormonal treatment. In 1989 Eliasson *et al*. (5) undertook a meta-analysis of the hormonal treatment of LAM. They identified 30 cases of LAM treated by hormonal manipulation. It is not clear if any of the thirty cases reviewed suffered from TSC and it is not yet known whether LAM with TSC and Lam without TSC are similar in their response to treatment. Unfortunately many of the cases lacked information on dosage, timing and duration of therapy making them ineligible for inclusion in the analysis (see Table 3). The remaining studies showed oophorectomy alone or

Table 3 Reported regimens of treatment before and after meta-analysis

Hormonal theraphy	Claimed success	Cases excluded*	Objective success
Progesterone alone	8/13	5	5/9
Oophrectomy alone	5/9	2	5/7
Tamoxifen alone	2/7	4	1/3
Androgen alone	0/1	0	0/1
Oophrectomy+progesterone	3/5	3	2/2
Oophrectomy and tamoxifen	0/1	1	0
Progesterone+tamoxifen	1/2	2	0
Oophrectomy, progesterone+Tamoxifen	1/3	1	1/2

*In sequential evaluation of each case, 10 cases were excluded because therapy was started too late in the course of disease; six additional cases were excluded due to lack of data on dosage; of cases remaining, two were excluded due to insufficient data to judge outcome of therapy.

in combination with progesterone to be the most successful therapeutic option, with seven out of nine cases showing stabilization or improvement. Progesterone alone was successful in five out of nine patients. None of the other regimes showed any significant benefit. Although this review suggests that hormonal manipulation might be beneficial in some patients the results need to be treated with caution. We would not recommend radioablation of the ovaries as a means of hormonal manipulation in patients with TSC: the genes involved in TSC are tumour suppressor genes so there is a theoretical risk that exposure to radiotherapy may increase the incidence and development of hamartomas.

It was previously thought that there was a relentless and severe deterioration after the onset of the disease. Average duration of survival was reported to be 4·8 years in 1971 (2). More recent studies estimate survival to be nearer to 10 years and there are even reports of apparent spontaneous resolution. Unfortunately few of the studies in which hormonal treatment was not undertaken gave follow-up information on their patients making it difficult to summarize the natural history of this condition.

LAM is undoubtedly rare and no study has attempted to estimate its prevalence within the general population. Although estimations have been made for its prevalence within the TSC population they have been made on biased groups and have not accounted for asymptomatic and possibly milder cases. LAM is a disease of women of child bearing age and a diagnosis of LAM in males and children should be treated with caution and should be confirmed by HRCT as a minimum and preferably by lung biopsy. Although the age of onset and age to diagnosis did not vary within the groups, the TSC patients did show a trend of presenting in a more insidious fashion with gradual onset of increasing dyspnoea as compared to the non-TSC patients who were more likely to present with a pneumothorax. Patients with TSC were also less likely to suffer chylothoraces. The reasons for these difference are not clear but they may reflect slight differences in the genetic pathogenesis of the two groups. It is difficult to summarise the natural history of this condition as there are no large cohort studies, but it does appear to be extremely variable. Likewise treatment regimes have varied greatly with poor long-term follow-up. Further research is required not only to elicit the natural history of this disease in greater detail, but also to determine the optimum treatment regime. This is likely to require a national surveillance programme.

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REFERENCES

1. Miller WT, Cornog JL, Sullivan MA. Lymphangiomyomatosis; clinical-roentgenologic-pathologic syndrome. *Am J Roentgenol* 1971; **111:** 565–572.
2. Dwyer JM, Hickie JB, Garvin J. Pulmonary tuberous sclerosis. Report of three patients and a review of the literature. *Q J Med* 1971; **157:** 115–125.
3. Castro M, Shepherd CW, Gomez MR, *et al*. Pulmonary tuberous sclerosis *Chest* 1995; **107:** 189–195.
4. Sobonya RE, Quan SF, Fleishman JS. Pulmonary lymphangioleiomyomatosis: Quantitative analysis of lesions producing airflow limitation. *Hum Pathol* 1985; **16:** 1122–1128.
5. Eliasson A, Phillips YY, Tenholder MF. Treatment of lymphangioleiomyomatosis: a meta-analysis. *Chest* 1989; **196:** 1352–1355.
6. Osborne JP. Diagnosis of tuberous sclerosis. *Arch Dis Child* 1988; **63:** 1423–1425.
7. Duckett JG, Lazarus A, White KM. Cutaneous masses, rib lesions and chylous plcural effussion in a 20-year old man. *Chest* 1990; **97:** 1227–1228.
8. Bowen J, Beasely SW. Rare pulmonary manifestations of tuberous sclerosis in children. *Ped Pulmonol* 1997; **23:** 114–116.
9. Nussbaum E, Groncy P, Finklestein J, *et al*. Early onset of childhood lymphangiomyomatosis. Clin Pediair 1988; **27:** 279–284.
10. Sakano T, Hamasaki T, Kawaguchi Y, *et al.* Pulmonary lymphangiomyomatosis in chilhood. *Hiroshima J Med Sci* 1989; **38:** 47–49.
11. Hughes E, Hodder RV. Pulmonary lymphangiomyomatosis complicating pregnancy. A case report. J *Reprod Med* 1987; **32:** 553–557.

12. Warren SE, Lee D, Martin V, *et al*. Pulmonary lymphangiomyomatosis causing bilateral pnuemothorax during pregnancy. *Ann Thorac Surg* 1993; **55:** 998–1000.
13. Sinclair W, Wright JL, Churg A. Lymphangioleiomyomatosis presenting in a postmenopausal woman. *Thorax* 1985; **40:** 465–476.
14. Baldi S, Papotti M, Valente M, *et al*. Pulmonary lymphangioleiomyomatosis in postmenoipausal women. *Eur Repir* J 1994; **7:** 1013–1016.
15. Dawson J. Pulmonary tuberous sclerosis. *Q J Med* 1954; **54:** 113–145
16. Graham M, Spelsberg T, Dines D, *et al*. Pulmonary lymphangioleiomyomatosis with particular reference to steroid receptor assay studies and pathologic correlation. *Mayo Clin Proc*. 1984; **59:** 3–11.
17. Capron F, Ameille J, Leclerk P, *et al*. Pulmonary lymphangioleiomatosis and Bournville's Tuberous sclerosis with pulmonary involvement: the same disease? *Cancer* 1983; **52:** 851–855.
18. Jourieaux V, Druelle S, Mayeux I, *et al*. Progesterone treatment in, chylothorax associated with pulmonary tuberous sclerosis. *Eur Respir J* 1999; **9:** 2423–2425.
19. Kitzsteiner AK Mallen RG. Pulmonary lymphangioleiomyomatosis: treated with castration. Cancer 1980; **46:** 2248–2249.
20. Murray DP, O'Sullivan JD. Pulmonary tuberous sclerosis responds to progesterone treatment. *Irish Med J* 1988; **157:** 196–197.